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Insomnia in epilepsy is associated with continuing seizures and worse quality of life

Mark Quigg[a,*], Sean Gharai[b], Jeff Ruland[b], Catherine Schroeder[b], Matthew Hodges[c], Karen S. Ingersoll[d], Frances P. Thorndike[d], Guofen Yan[e], Lee M. Ritterband[d]

[a] Department of Neurology, Comprehensive Epilepsy Program, University of Virginia, Charlottesville, VA 22908, USA
[b] College of Arts and Sciences, University of Virginia, Charlottesville, VA 22908, USA
[c] School of Medicine, University of Virginia, Charlottesville, VA 22908, USA
[d] Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA 22908, USA
[e] Department of Public Health Sciences, Biostatistics Section, University of Virginia, Charlottesville, VA 22908, USA

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ABSTRACT

Purpose: To evaluate how insomnia is associated with seizure control and quality of life in patients with epilepsy.
Methods: Consecutive patients with epilepsy attending clinical visits were surveyed with the Insomnia Severity Index (ISI). Patients had to be treated with at least one anticonvulsant and could not have had documented psychogenic pseudoseizure. The presence or absence of seizures and quality of life (QOLIE-P-10) within the past 4 weeks was recorded. Other variables included demographic and clinical data, sleep-wake timing, the Hörne–Östberg Morningness–Eveningness Questionnaire (MEQ), sleepiness (Epworth Sleepiness Scale (ESS), and mood (Center for Epidemiologic Studies Depression Scale, CES-D).
Results: 207 patients completed surveys. 43% had clinically significant insomnia, and 51% had at least mild insomnia. 58% were seizure free. Mean ISI scores were significantly worse for those with continuing seizures, and more severe ISI scores correlated strongly with worse QOL. Younger age, shorter duration of epilepsy, use of sedative/hypnotics, medical and sleep comorbidities, delayed sleep timing and chronotype, excessive sleepiness, and depression were all associated with more severe insomnia. Those with unexpected health care visits over the most recent 4 weeks had worse insomnia. After adjustment for these covariates, more severe insomnia remained significantly associated with lack of seizure freedom and with worse QOL.
Significance: Insomnia is common in epilepsy, and is associated with short term poor seizure control and worse QOL. Future studies must evaluate cause-and-effect relationships. Assessment of insomnia may be important in the comprehensive care of epilepsy and may influence control of epileptic seizures.

1. Introduction

Approximately 30% of adults complain of symptoms of insomnia, and 10% experience insomnia chronically (Morin and Benca, 2010; Morin et al., 2006). Insomnia is associated with impaired mood, poorer quality of life, and more health care utilization (Morin and Benca, 2010; Morin et al., 2006). Insomnia is costly with direct medical costs of insomnia in the US estimated at $13 billion/year in physician visits, prescriptions and procedures (Walsh and Engelhardt, 1995). People with insomnia spend $1200 more in direct health care expenses than patients without insomnia (Ozminkowski et al., 2007).

Problems with sleep are common in patients with epilepsy (de Weerd et al., 2004; Malow et al., 2000; Manni et al., 2003; Vendrame et al., 2013; Xu et al., 2006) with prevalence estimates ranging from 24 to 55%. However, the effects of insomnia in patients with epilepsy regarding control of seizures remain unclear with studies disagreeing on whether seizures are more frequent or not among those with insomnia (Piperidou et al., 2008; Vendrame et al., 2013). The hypothesis that sleep disturbances worsen seizure control has been supported by studies demonstrating worsened control in those with sleep apnea and improvement in control after treatment

Abbreviations: QOL, quality of life; TIB, time in bed; MSF, mean sleep time on free days; ISI, Insomnia Severity Index; AED, antiepileptic drug; MEQ, Morningness–Eveningness Questionnaire; ESS, Epworth Sleepiness Scale; CES-D, Center for Epidemiological Studies Depression Scale.

* Corresponding author. Tel.: +1 434 924 5312; fax: +1 434 982 1726.
E-mail address: quigg@virginia.edu (M. Quigg).

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(Malow et al., 2008; Vendrame et al., 2011). Although several studies have established that insomnia correlates with impaired quality of life (de Weerd et al., 2004; Piperidou et al., 2008; Vendrame et al., 2013; Xu et al., 2006), effects on health care use in the setting of epilepsy are unknown. Furthermore, chronotype – the circadian expression of the rest-activity cycle – may affect or promote insomnia (Sack et al., 2007), but has not been evaluated in patients with epilepsy and sleep disturbances. Patients with epilepsy, without regard to sleep quality, have been shown to prefer phase-advanced activity compared with non-epileptic controls (Hofstra et al., 2010).

The purposes of this study are (1) to characterize the prevalence, severity, and characteristics of insomnia in a sample of patients with epilepsy in a tertiary epilepsy specialty clinic, (2) to determine the clinical, sleep/schedule, and neurocognitive factors that are associated with insomnia in epilepsy, and (3) to evaluate how insomnia is associated with seizure control and quality of life.

2. Material and methods

2.1. Participants

This IRB-approved study consisted of standardized, prospective data collection from a convenience sample of consecutive patients (assuming sufficient staff availability) seen in the University of Virginia Comprehensive Epilepsy Program from September 2014 to March 2015. Inclusion criteria were (1) diagnosis of epilepsy (defined as >1 spontaneous epileptic seizure) based on expert evaluation of the clinical gestalt of symptoms, EEG findings, and neuroimaging, (2) use of at least one daily AED for at least one month before the survey, and (3) literacy in English. Exclusions were (1) previous diagnosis of nonepileptic pseudoseizure documented through video-EEG monitoring, and (2) cognitive inability of the patient to answer the survey.

Patients were instructed to limit responses to symptoms and status within the previous four weeks. The main predictor variable was the Insomnia Severity Index (ISI), a seven-item, validated, Likert scale instrument ranging from 0 to 28 with higher scores indicating more severe symptoms. A cut-off score ISI $\geq$8 suggests mild insomnia, and ISI $\geq$10 suggests clinically significant insomnia (Morin et al., 2011).

The main outcome variable was seizure-freedom. We asked patients to either recall or extract from diaries seizure frequency in the most recent 4 weeks. We limited seizure information to a four week window to correspond with the limited time-window of survey data. We divide patients into those with no seizures over that interval compared to a control group of those with $\geq$1 seizures. The other outcome examined was quality of life (QOL) assessed with the quality of life in epilepsy survey (QOLIE-10-P, (Cramer et al., 1996), range 12–63, with higher scores designating a more favorable health state or better QOL).

Other variables surveyed included *demographics* (age, sex), *clinical information* [epilepsy syndrome (partial or generalized), duration of epilepsy, the number of prescribed AED and sedative-hypnotic medications, and the presence of other comorbid diagnosed sleep disorders or disorders that may appear with insomnia (mood or anxiety disorder, obesity defined as BMI $\geq$35, chronic headache or pain, obstructive sleep apnea treated with positive airway pressure, congestive heart failure or chronic obstructive pulmonary disease, parasomnias, or narcolepsy)]. *Sleep habits, scheduling, and symptoms* were assessed by obtaining habitual work-day and off-day bed times (defined as time the patient lay in bed) and wake times (time arising from bed) that were used to calculate habitual time in bed (TIB) and mid-sleep time on free nights (MSF, the clock time one-half way between bedtime and wake time on non-working days, a quantity that correlates with other measures of circadian preferences; later MSF indicates delays in circadian phase) (Zavada et al., 2005). Circadian preferences were assessed with the Hörne–Östberg Morningness–Eveningness Questionnaire, MEQ (Horne and Ostberg, 1976) in which higher scores indicate morning preference. Daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS) with higher scores indicating increased sleepiness (Johns, 1991). Work status was coded as working part- or full-time versus unemployed. *Mood* was assessed with the Center for Epidemiologic Studies Depression Scale, CES-D (Radloff, 1977) with higher scores designating more depression. Unexpected *health care use* was assessed by asking if the patient had seen a health care provider unexpectedly in the most recent four weeks (inpatient or outpatient physician assessment excluding the survey visit). Patients were guided through questions by interviewers who clarified questions if needed but remained blinded to patient responses.

2.2. Data analysis

We performed correlation analysis to examine the bivariate associations between ISI and each of the study variables. Pearson's correlation coefficient was used for continuous variables with ISI scores. Two-sample *t*-test was used for the dichotomous variables with ISI scores.

We then examined the associations of ISI and the outcomes (seizure and QOL) with and without adjustment for multiple covariates. Specifically, for the main outcome of seizure occurrence, we first used a logistic regression model of those without seizures compared to those with continuing seizures. This analysis included ISI as a single covariate and then expanded the model to include the covariates that were significantly correlated with ISI in the correlation analysis as described above. Similarly, we used linear regression for QOL. Significant results are interpreted at two-sided significance level of 0.05.

3. Results

212 patients were asked to participate. Four declined, and one survey was interrupted by a seizure and remained incomplete. Of the remaining 207 patients (for a participation rate of 98%), the mean $\pm$ SD ISI score was 8.5 $\pm$ 6.7 (Fig. 1A). 110 (43%) reported clinically significant insomnia as determined by a cutoff score on the ISI $\geq$10. 109 (51%) of patients had at least mild insomnia as indicated by an ISI score of $\geq$8.

Of the 207 patients, 121 (58%) were seizure-free. The 42% of patients who were not seizure free had significantly higher ISI scores (and therefore, more severe insomnia) than seizure-free patients (Student's *t* test *p* value < 0.0001, Fig. 1B). QOLIE-10-P scores inversely correlated with ISI scores indicating that poorer quality of life is associated with more severe insomnia (Pearson's $r = -0.467$, $p < 0.0001$, Fig. 1C).

Table 1 shows the results of correlation analysis for ISI scores with the study variables. Both patient age and duration of epilepsy correlated negatively with ISI, indicating that younger patients or those with shorter durations of epilepsy had worse ISI scores. Neither sex nor epilepsy syndrome showed associations with ISI. Those taking one versus more than one AED did not differ by mean ISI scores. On the other hand, sedative-hypnotic use was associated with significantly higher ISI scores. The presence of co-morbidities was associated with significantly worse ISI scores with almost half (48%) reporting a comorbidity. Mood/anxiety disorder was the most common (23%) comorbidity reported.